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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/436,347	11/09/1999	CHRISTINE A. WHITE	012712-643	6491

909 7590 01/31/2005

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EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/436,347	WHITE ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments and Arguments

1. Claims 1-18 are pending.

Claims 1, 7, 12, 14 and 17 have been amended.

Claims 19-27 have been cancelled.

Claims 1-18 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

3. The rejection of claim 7 under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials is withdrawn in light of Applicants' arguments.

4. The rejection of claim 7 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of the claim amendment.

Claim Rejections - 35 USC § 102

5. The rejection of claims 1-4 and 7-18 under 35 U.S.C. 102(e) as being anticipated by US Patent number 6,455,043 (effective filing date August 11, 1998) is withdrawn in light of Applicants' arguments. Claims 19-27 have been cancelled.

Claim Rejections - 35 USC § 103

6. The rejection of claims 1-19 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent number 6,455,043 (effective filing date August 11, 1998) is withdrawn in light of Applicants' arguments. Claims 19-27 have been cancelled.

New Grounds of Objection

Specification

7. The use of the trademark, RITUXAN® (rutximab) antibody has been noted in this application, see page 3, 6, 10 and 12. It should be capitalized wherever it appears and be accompanied by the generic terminology. Applicants should review the entire specification for similar errors.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

8. The rejection of claims 1-12 and 14-18 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. Claims 19-27 have been cancelled. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTION.**

Applicants have amended claims 1, 12 and 14 to include the recitation "...hematologic malignancy is characterized by a white blood cell count from 4 x 10^9 to about 200 x 10^9 white blood cells per liter of blood, ". Applicants assert in the Remarks submitted October 19, 2004 "[t]he Examiner acknowledges the Applicants' specification at pages 12-13 provides a teaching of an example of a patient with high levels of circulating tumor cells characterized,,,by a white blood cell count ranging from 4 x 10^9 to about 200 x 10^9 white blood cells per liter of blood", see page 9, last paragraph of Remarks. This is a mischaracterization of what the Examiner noted on page 5, last paragraph of the Action mailed April 19, 2004. The Examiner stated "[w]hat is clear...is *the medium with blood cell count was 40 x* 10^9 per liter and that range encompassed 4-200. The specification does not provide support that Applicants have contemplated that the malignancy has *at least* 40 x 10^9 white blood cells per liter." Applicants have not established a nexus between high levels of circulating tumor cells with the range of white blood cell count from about 4 x 10^9 to about 200 x 10^9. Moreover, in an attempt to

evidence support of a hematologic malignancy having the specified white blood cell count Applicants refer the Examiner to Byrd et al. (Journal of Clinical Oncology 17(3): 791-795, March 1999. The Examiner has retrieved the article and read it. It is not noted wherein the referenced article an art known fact is established regarding a hematologic malignancy's white blood cell count is the established range of x to x.

For the reasons of record and the analysis provided above the 112, 1st new matter rejection is maintained.

9. Claims 1-12 and 14-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1, 12 and 14 recite "...hematogical malignancy with high levels of circulating tumor cells in the blood". It is not clear what amount of tumor cells is qualified as high. There is no reference point as to what to base the high number. It is not clear within what range high numbers should be assessed. Moreover, it is not clear which types of tumor cells the claims address. Tumor cells could be red blood cells, white blood cells, as well as cells from a primary cancer that have now metastasized. Accordingly, the metes and the bounds of the claimed invention cannot be determined.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

11. Claim 13 is rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent number 6,090,365 (field November 18, 1997). U.S. Patent #6,090,365 discloses methods for treatment of chronic lymphocytic leukemia (CLL), chronic myeloblastic leukemia and lymphomas by administration of a B-cell specific antibody, antibody B1, see the abstract; column 5, lines 25-35; column 7, lines 24-47; and column 13, lines 40-61. It is reasonable to conclude that B-prolymphocytic leukemia (B-PLL) and transformed non-Hodgkin's lymphoma would also be treated using the disclosed methodology to achieve the reduction in circulating tumor cells in light of the patent's disclosure of the successful treatment of the listed leukemias and lymphomas.

12. Claims 1-4, 6, 7, 9 and 12-17 are rejected under 35 U.S.C. 102(a) as being anticipated by McLaughlin et al. (Journal of Clinical Oncology 16(8): 2825-2833, August 1998/ IDS reference B1, submitted October 19, 2004). McLaughlin discloses a method of treating patients with relapsed indolent lymphoma and patients with chronic lymphocytic leukemia (CLL) having less than 5 $x10^9$/L lymphocytes comprising the administration of a chimeric anti-CD20 monoclonal antibody, rituximab (IDEC-C2B8), see title and Patients and Methods section on page 2826, column 1.. CLL patients with 4 x 10^9L are with Applicants' stated range listed in claim 1. All of the patients were given an antibody dose of 375mg/m^2 intravenously once weekly for a total of four infusions, see abstract and page 2826, column 1, Therapy section. "The initial infusion rate was 50mg/h, with subsequent infusion rate increase...", see cited Therapy section. Moreover, with the administration of the said antibody in the disclosed methodology inherently there would be a reduction in circulating tumor cells.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over McLaughlin et al. (Journal of Clinical Oncology 16(8): 2825-2833, August 1998/ IDS reference B1, submitted October 19, 2004), in view of U.S. Patent number 6,682,734

(effective filing date November 13, 1992) and EP document 0 510 949 A2 (April 23, 1991). The teachings of McLaughlin were presented in the 102(a) rejection. McLaughlin does not teach the claimed method, wherein the antibody is administered at a dosage ranging from 0.1 to 30 mg/kg and particularly administered at an initial dose of 100mg/m^2 and the remainder of a 375mg/m^2 is administered on the following day. McLaughlin also does not teach the method inclusive of an additional treatment such as radiation, chemotherapy or lymphokines administration.

However, U.S. patent #6,682,734 teaches the administration of effective dosages or therapeutically effective amounts of immunologically active chimeric anti-CD20 antibodies from about 0.001 to about 30 mg/kg body weight and suggests that the skilled artisan could easily assess a suitable dosage for a particular patient, see column 7, lines 16-26. The patent also teaches treatment with chemotherapeutic agents such as cyclophosphamide, vincristine, prednisone and doxorubicin (CHOP) and radionuclides, see column 8, line 11-column 9, line 7 and column 30, lines 32-43. Moreover, EP 0 510 949 A2 teaches conjugate moieties comprising antibodies and interleukins 1-10, GM-CSF, TNF and interferons and their subsequent administration for treatment of leukemias and lymphomas, see column 3, lines 27-47; column 5, lines 23-31; bridging paragraph of columns 5 and 6.

It would have been *prima facie* to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of McLaughlin, the patent and the EP document in order to efficaciously treat cancer. One of ordinary skill in the art would have been motivated to combine the teachings of all the documents, McLaughlin,

the patent and the European document because McLaughlin cites there has been "...evidence of synergism between [rituxumab] and some chemotherapeutic agents", it is art known that toxins have been conjugated to antibodies, as well as a variety of radionuclides for targeted immunotherapy, and the conjugates may be used to specifically destroy cells associated with a pathogenic condition (i.e. leukemias and lymphomas), see McLaughlin page 2831, column 2, last paragraph; the patent, column 3, lines 55-58 and column 8, line 11-column 9, line 22; and EP document, abstract and column 5, lines 23-31.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571)272-0831. The examiner works a flexible schedule, however she can normally be reached between the hours of 6:30 am to 5:30 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
24 January 2005